

(FILE 'HOME' ENTERED AT 14:55:30 ON 13 JUL 2000)

FILE 'CAPLUS' ENTERED AT 14:55:43 ON 13 JUL 2000

L1 1567 S RACEMIZ?(L) (AMINO(W)ACID?)
L2 144 S L1 AND (PROLIN? OR HOMOPROLIN?)
L3 2 S L2 AND PIPERIDIN?

AN 1967:473852 CAPLUS
 DN 67:73852
 TI Studies on optically active **amino acids**. XII.
 Synthesis, resolution and **racemization** of bicyclic .alpha.-amino
 ketones
 AU Kunieda, Takehisa; Koga, Kenji; Yamada, Shunichi
 CS Univ. Tokyo, Tokyo, Japan
 SO Chem. Pharm. Bull. (1967), 15(3), 337-44
 CODEN: CPBTAL
 DT Journal
 LA English
 GI For diagram(s), see printed CA Issue.
 AB cf. CA 67: 54417t. A mixt. of 32 g. **L-proline** Et ester (I)
 [[.alpha.]8D -43.5.degree. (c. 3.8, all in EtOH)] and 50 ml. freshly
 distd. CH₂:CHCO₂Et was refluxed 6.3 hrs. in 40 ml. EtOH, low boiling
 fractions were removed in vacuo, and the residue was distd. to yield 47.2
 g. Et (-)-2-(ethoxycarbonyl)-1-pyrrolidinepropionate (II), b₂
 113-20.degree.; [.alpha.]15D -66.4.degree. (c 1.7). II (47.2 g.) in 150
 ml. abs. PhMe was added to a suspension of alc. free NaOH (from 4.7 g.
 Na) in 100 ml. abs. PhMe. The mixt. was refluxed 1.5 hrs. with stirring
 under N, cooled, extd. with .apprx.200 ml. H₂O. The aq. ext. was treated with
 230 ml. concd. HCl, the mixt. heated 1.7 hrs. on a water bath until the
 FeCl₃ test was neg. The mixt. was made strongly basic with K₂CO₃, extd.
 with ether, and the ext. dried and distd. to yield 9.5 g.
 hexahydro-1H-pyrrolizin-1-one (III), b₄ 65.degree.; [.alpha.]9D
 -49.7.degree. (c 2.5) (unstable in air); [.alpha.]9D -59.2.degree. (c
 2.3, dioxane) [picrate m. 165-7.degree. (EtOH); oxime HCl salt, m.
 172-3.degree. (EtOH), [.alpha.]25D .+- 0.degree. (c 1); oxime m.
 158-60.degree.]. L-Pipecolic acid Et ester (3.5 g.) and 20 ml. freshly
 distd. CH₂:CHCO₂Et in 20 ml. EtOH was refluxed 5.5 hrs. to yield 3.4 g.
 Et (-)-2-(ethoxycarbonyl)-1-**piperidinepropionate** (IV), b_{0.5}
 127-32.degree.; [.alpha.]27D -26.7.degree. (c 2.1). IV (3.4 g.) on
 treating with NaOEt (as for III) yielded 42% hexahydro-1(5H)-indolizinone
 (V), b₁₋₂ 65-70.degree.; [.alpha.]25D .+- 0.degree. (c 5.8) (unstable
 liquid) [oxime m. 115-16.degree. (iso-PrOH-iso-Pr₂O); picrate m.
 170-1.degree. (Me₂CO); picrolonate m. 174-5.degree. (EtOH)]. dl-V (5 g.)
 and 11.5 g. d-3-bromo-8-camphorsulfonic acid (Va) in 20 ml. Me₂CO was
 kept overnight in a refrigerator to yield 3.2 g. (-)-hexahydro-1(5H)-
 indolizinone 3-bromo-8-camphorsulfonate, m. 160-1.5.degree. (Me₂CO);
 [.alpha.]15D 38.7.degree. (c 1.25, H₂O). The salt (2 g.) in 5 ml. H₂O
 was made strongly basic with K₂CO₃ and extd. with C₆H₆ to yield 0.46 g.
 (-)-V,
 b₁₋₂ 68-70.degree.; [.alpha.]24D -105.degree. (c 4.6); [.alpha.]24D
 -107.3.degree. (c 0.8, dioxane) [oxime HCl salt m. 193-4.degree.
 (EtOH-iso-Pr₂O) [.alpha.]24D -22.0.degree. (c 1, H₂O)]. The enantiomeric
 base V, b₅ 80.degree.; [.alpha.]20D 30.degree. (c 1.28) was also obtained
 on similar treatment of the mother liquor. IV (7.5 g.) was added to a
 suspension of NaOEt (from 0.7 g. Na) in 80 ml. abs. PhMe, the mixt.
 refluxed 2.5 hrs. under N, cooled and extd. with 40 ml. H₂O. The aq.
 ext.

was neutralized by adding Dry Ice or HOAc, extd. with ether and CH₂Cl₂, and the combined ext. evapd. in vacuo to yield 1.5 g. Et octahydro-1-oxo-2-indolizine-carboxylate (VI), b0.6 105-7.degree.; [.alpha.]_{27D} +-. 0.degree. (c 3.8). A soln. of 19 g. II and 30 g. Et 4-bromobutyrate in 60 ml. Me₂CO was stirred 3.5 hrs. under N in the presence of 20 g. anhyd. K₂CO₃ to yield 28.5 g. Et

(-)-2-ethoxycarbonyl-1-pyrrolizinebutyrate (VII), b0.1 132.degree.; [.alpha.]_{13D} -63.7.degree. (c 0.54). Treatment of 15 g. VII with NaOEt (as for VI) yielded 3 g. Et (-)-octahydro-8-oxo-7-indolizinecarboxylate (VIII), b0.05 99-102.degree.; [.alpha.]_{19D} -25.1.degree. (c 2.7); the PhMe layer yielded 4.2 g. starting compd. VII, indicating the occurrence of racemization. VIII (3 g.) was decarboxylated by heating 25 hrs. on a water bath with 20 ml. 10% HCl to yield 1.3 g. hexahydro-8(5H)-indolizinone (IX), b5 65-7.degree.; [.alpha.]_{16D} +-.0.degree. (l = 1 cm.; neat) [oxime m. 117-18.degree. (iso-PROH); picrate m. 147-8.degree. (EtOH)]. A soln. of 3.6 g. dl-IX and 8.5 g. Va in 40 ml. Me₂CO was left 2 days at room temp. to give 8.3 g. of the corresponding Va salt monohydrate, m. 130-1.degree.; [.alpha.]_{17D} 56.8.degree. (c 2.07, H₂O); the amino ketone (b15 90-8.degree.) recovered from the salt was optically inactive. Alternatively, 5.6 g. dl-IX and 9.6 g. d-10-camphorsulfonic acid in 60 ml. Me₂CO and 20 ml. abs. ether was kept overnight in the refrigerator to yield 5 g. (+)-hexahydro-8(5H)-indolizinone 10-camphorsulfonate monohydrate, m. 97-101.degree. (Me₂CO); [.alpha.]_{15D} 16.0.degree. (c 2, H₂O); the amino ketone [.alpha.]_{13D} 0.93.degree. (c 4.3) [oxime HCl salt m. 176.degree. (EtOH); [.alpha.]_{14D} 7.9.degree. (c 1.7, H₂O)]. Ethyl (+)-2-ethoxycarbonyl-1-piperidinebutyrate (X) (13 g.) (b17 100.degree.; [.alpha.]_{28D} 13.3.degree. (c 3.12)) was obtained from 10.2 g. D-pipecolic acid Et ester in the same way as VII. Treatment of X with NaOEt (as for I) yielded 50% hexahydro-2H-quinolizin-1-(6H)-one (XI), b3-5 80-90.degree.; [.alpha.]_{30D} +-.0.degree. (c 10 [picrate m. 166-7.degree. (EtOH); semicarbazone, m. 214.degree. (EtOH); oxime HCl salt m. 214.degree. (EtOH-iso-Pr₂O). X (4 g.) was subjected to the Dieckmann cyclization using NaOEt (from 0.35 g. Na) in the same way as VI to yield 0.85 g. Et (+)-octahydro-1-oxo-2-quinolizine-carboxylate, b0.15 109-15.degree.; [.alpha.]_{32D} 38.6.degree. (c, 3.0). A soln. of 5.8 g. dl-XI and 12 g. Va in 30 ml. Me₂CO was left overnight at room temp. to yield 4 g. (-)-hexahydro-2H-quinolizin-1(6H)-one 3-bromo-8-camphorsulfonate, m. 195-6.degree.; [.alpha.]_{20D} 61.2.degree. (c 2, H₂O), which yielded (-)-XI, b8 93-5.degree.; [.alpha.]_{10D} -37.degree. (c 5.5); [.alpha.]_{22D} -31.7.degree. (c 3.3, isooctane); Analogous treatment of the mother liquor afforded the enantiomeric (+)-XI, [.alpha.]_{20D} 22.7.degree. (c 1.88) [oxime HCl salt; [.alpha.]_{20D} 38.6.degree. (c 1, H₂O)]. L-Phenylalanine was subjected to the Pictet-Spengler reaction by the method of Archer (CA 46: 2548i) to give 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride, which on esterification (SOCl₂-EtOH) afforded 60% Et (-)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (XII), b0.2 115-21.degree.; [.alpha.]_{20D} -76.8.degree. (c 0.7) [HCl salt, m. 203-5.degree. (decompn.) (EtOH); [.alpha.]_{20D} -85.7.degree. (c 1.2, H₂O); picrate m. 198-9.degree. (EtOH)]. Ethyl (-)-3-ethoxycarbonyl-1,2,3,4-tetrahydro-2-isoquinolinebutyrate (XIII) [b2-3 180-90.degree.; [.alpha.]_{28D} -7.4.degree. (c 5)] was prepd. from the ester XII in 50% yield according to the modified procedure described for VII. XIII (12.1 g.) and 0.91 g. NaH in 120 ml. abs. dioxane was gently refluxed 1 hr. under N to yield 5.5 g. Et (-)-1,3,4,6,11,11a-hexahydro-1-oxo-2H-benzo(b)quinolizine-2-carboxylate (XIV), m. 79-9.5.degree.; [.alpha.]_{28D} -13.3.degree. (c 1.5). Decarboxylation of 1.5 g. XIV by heating 1.5 hrs. in 15 ml. 10% HCl yielded 0.65 g.

3,4,11,11a-tetrahydro-2H-benzo[b]quinolizin-1(6H)-one (XIVa), m.
96-8.degree.; [.alpha.]_{25D} .+-.0.degree. (c 1.5). The rate consts. and
half-times for racemization of III, V, IX, and XI were detd. under
various
conditions, at 20.degree., and in aq. EtOH. III was found to be
racemized
very rapidly, while in HCl, no racemization was observed.

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2000 ACS

AN 1967:454417 CAPLUS

DN 67:54417

TI Optically active **amino acids**. XIII.

Racemization of N-benzoylanilides of optically active
proline and pipecolic acid

AU Kunieda, Takehisa; Koga, Kenji; Yamada, Shunichi

CS Univ. Tokyo, Tokyo, Japan

SO Chem. Pharm. Bull. (1967), 15(3), 350-1

CODEN: CPBTAL

DT Journal

LA English

AB CA 67: 22124d. Effect of ring size on rate of **racemization** of
monocyclic .alpha.-**amino acid** derivs. such as
(-)-1-benzoyl-2-pyrrolidinecarboxanilide (I) and (+)-1-benzoyl-2-
piperidinecarboxanilide (II) is studied. N,N'-
Dicyclohexylcarbodiimide (2 g.) was added to a soln. of 2.1 g.
N-benzoyl-L-**proline** (III) and 0.93 g. PhNH₂ in 45 ml. CH₂Cl₂,
stirred at room temp. 3.5 hrs., clarified by filtration, washed with aq.
NaHCO₃ soln., and concd. to give 1.7 g. I, m. 185-6.degree., [.alpha.]_{14D}
-115.6.degree. (c 1.6, EtOH). A mixt. of 6.57 g. III and 3.03 g. Et₃N in
120 ml. abs. PhMe at -7 to -5.degree. was treated with 3.26 g. ClCO₂Et,
kept at -5.degree. for 25 min., treated with 2.8 g. PhNH₂, allowed to
stand overnight, clarified by filtration, washed with dil. HCl and aq.
NaHCO₃ soln., and concd. to give 5.5 g. I. II, m. 167-9.degree.,
[.alpha.]_{18D} 55.8.degree. (c 1.04, EtOH), was similarly prepd. Their

rate

of **racemization** was measured polarimetrically in Me₂SO soln. at
40 .+-. 0.5.degree., using 3 moles of NaOEt as a base to show that I
racemized 6 times faster than II.

=> s methyl(1)pheni?

515607 METHYL
2391 PHENI?
L5 130 METHYL(L) PHENI?

=> s 15 and racemiz?

6537 RACEMIZ?
L6 0 L5 AND RACEMIZ?

=> s 15 and threo?

41378 THREO?
L7 6 L5 AND THREO?

=> d bib abs 1-6

L7 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2000 ACS
AN 2000:113124 CAPLUS
DN 132:151683
TI Enantioselective synthesis of **methyl phenidate**
IN Winklter, Jeffrey David; Axten, Jeffrey M.; Krim, Lori
PA The Trustees of the University of Pennsylvania, USA
SO U.S., 11 pp.
CODEN: USXXAM

DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6025502	A	20000215	US 1999-273144	19990319
OS	MARPAT 132:151683				
AB	The D- threo isomer of Me phenidate is prepd. selectively by reaction of N-BOC piperidine (I) with PhC(:N2)COOMe (II) in the presence of dirhodium tetrakis[methyl 2-oxopyrrolidine-5(R)-carboxylate] as catalyst. Related compds. can be prepd. by using, e.g., N-BOC pyrrolidine, instead of I and, e.g., Et phenyldiazoacetate, Me 1-naphthyldiazoacetate, or Et 1-naphthyldiazoacetate instead of II.				

RE.CNT 25

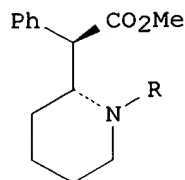
RE

(4) Anon; WO 9727176 1997 CAPLUS
(5) Anon; WO 9727176 1997 CAPLUS
(6) Anon; WO 9728124 1997 CAPLUS
(7) Anon; WO 9735836 1997 CAPLUS
(8) Anon; WO 9825902 1998 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2000 ACS
AN 1999:392473 CAPLUS
DN 131:157698
TI Enantioselective Synthesis of D-**threo**-Methylphenidate
AU Axten, Jeffrey M.; Ivy, Robert; Krim, Lori; Winkler, Jeffrey D.
CS Department of Chemistry, The University of Pennsylvania, Philadelphia, PA,

19104, USA
SO J. Am. Chem. Soc. (1999), 121(27), 6511-6512
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
OS CASREACT 131:157698
GI



AB The hydrochloride of Me D-**threo**-phenidate I (Ritalin) (R = H) was prepd. enantioselectively in two steps from N-Boc piperidine and Me phenyldiazoacetate by an enantioselective C-H insertion reaction catalyzed by the dirhodium catalyst Rh₂(5R-MEPY)₄ to give the phenidate I (R = Boc) in 64% yield. Treatment of I (R = Boc) with methanolic HCl and two recrystns. from 1:1 ethanol:diethyl ether gave I as its hydrochloride in 26% yield (68% yield before recrystn.).

RE.CNT 32

RE

- (2) Axten, J; J Org Chem 1998, V63, P9628 CAPLUS
- (3) Calter, M; Curr Org Chem 1997, V1, P37 CAPLUS
- (4) Dakin, L; Tetrahedron Lett 1998, V39, P8947 CAPLUS
- (5) Davies, H; J Am Chem Soc 1997, V119, P9075 CAPLUS
- (6) Dieter, R; J Org Chem 1997, V62, P7726 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2000 ACS

AN 1998:482482 CAPLUS

DN 129:202841

TI Enzymic resolution of (.+-.)-**threo**-methylphenidate

AU Prashad, Mahavir; Har, Denis; Repic, Oljan; Blacklock, Thomas J.; Giannousis, Peter

CS Chemical and Analytical Development, Process Research and Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, 07936, USA

SO Tetrahedron: Asymmetry (1998), 9(12), 2133-2136

CODEN: TASYE3; ISSN: 0957-4166

PB Elsevier Science Ltd.

DT Journal

LA English

OS CASREACT 129:202841

AB The resolu. of (.+-.)-**threo**-methylphenidate by enzymic hydrolysis with .alpha.-chymotrypsin or subtilisin carlsberg to afford (2S,2'S)-(-)-**threo** and (2R,2'R)-(+)-**threo**-methylphenidate hydrochlorides in high enantiomeric purities is described.

L7 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2000 ACS

AN 1981:525869 CAPLUS

DN 95:125869

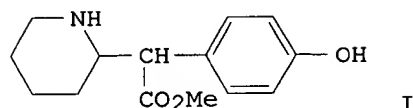
TI Synthesis and pharmacology of hydroxylated metabolites of **methyl phenidate**

AU Patrick, Kennerly S.; Kilts, Clinton D.; Breese, George R.

CS Sch. Med., Univ. North Carolina, Chapel Hill, NC, 27514, USA

SO J. Med. Chem. (1981), 24(10), 1237-40

DT Journal
LA English
GI



AB Me **threo**-dl- (I) [78708-74-4] and erythro-dl-p-hydroxymethylphenidate-HCl (II) [78708-67-5] and their resp. deesterified products III [78708-75-5] and IV [78708-76-6] were synthesized and tested for dopaminergic activity in rats. The locomotor response to I was greater than that to II, ritalin (V) [298-59-9], or erythro-dl-methylphenidate-HCl [23644-60-2], suggesting that I may play a role in the pharmacol. of V in the hyperkinetic syndrome in children. **threo**-dl-Ritalinic acid-HBr [78708-68-6], erythro-dl-ritalinic acid-HBr [78779-59-6], III, and IV produced small increases in locomotor activity relative to their Me esters and the responses were not appreciably affected by stereochem. or para-hydroxylation.

L7 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2000 ACS

AN 1975:118724 CAPLUS

DN 82:118724

TI Metabolism and disposition of **methyl phenidate**-14C: Studies in man and animals

AU Faraj, B. A.; Israili, Z. H.; Perel, J. M.; Jenkins, M. L.; Holtzman, S. G.; Cucinell, S. A.; Dayton, P. G.

CS Dep. Med., Emory Univ., Atlanta, Ga., USA

SO J. Pharmacol. Exp. Ther. (1974), 191(3), 535-47

CODEN: JPETAB

DT Journal

LA English

GI For diagram(s), see printed CA Issue.

AB 14C-labeled **threo**-dl-methylphenidate-HCl (**threo**-dl-I-HCl) [23655-65-4] was extensively metab. in man, dog, rat and mouse but with pronounced species differences. In human subjects, blood plasma levels of I were also much higher after i.v. than after oral administration. After oral administration, 50 and 90% of the 14C was excreted in urine in 8 and 48 hrs, resp. This suggests essentially complete absorption of I. The main urinary metabolite was the deesterified product, **threo**-dl-ritalinic acid [54631-24-2], accounting for 80% of the dose. Upon i.v. administration of I to dogs, 50-60% of the radioactivity was excreted in 7 hr urine. The major metabolites in dog urine were ritalinic acid and **threo**-dl-2-phenyl-2-(2'-piperidyl-6'-one)acetic acid [54593-31-6]. In rats, both after i.p. and oral administration of I, 50-60% of the 14C was eliminated in urine and 30-40% in feces within 48 hrs. Significant biliary excretion of 14C (25-30% in 12 hrs) was found bile-cannulated rats. The major metabolites in rat urine besides ritalinic acid were **threo**-dl-2-(p-hydroxyphenyl)-2-(2'-piperidyl)acetic acid [54593-32-7], its methyl ester [54593-35-0] and its glucuronide conjugate [54642-79-4]. The locomotor activity of I, certain metabolites and N-acetyl-**threo**-dl-methylphenidate [54593-33-8] was studied in mice.

L7 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2000 ACS

AN 1969:96027 CAPLUS

DN 70:96027